Available online at www.annclinlabsci.org

Review: Evaluating Selenium Poisoning

Kern L. Nuttall
Consultant in Laboratory Medicine, Bellingham, Washington

Abstract. Selenium poisoning in humans is reviewed from the perspective of the clinical laboratory. While evaluation of selenium poisoning is straightforward when the analytic results are markedly elevated and the patient is acutely symptomatic, distinguishing toxic from non-toxic elevations is a more frequent issue and more challenging. A significant problem is that selenium is determined as its total concentration in spite of the fact that different chemical forms of selenium have different toxic potentials. In the published reports reviewed herein, serum selenium concentrations span the following ranges: 400-30,000 µg/L associated with acute toxicity, 500-1400 µg/L associated with chronic toxicity, and <1400 µg/L free of toxicity; the category is determined by signs and symptoms in the patient. Most reports that describe acute selenium poisoning involve ingestion of inorganic compounds such as selenious acid, found in gun-bluing agents, and fatalities that occur within the first day are associated with postmortem blood selenium levels >1400 µg/L. Tissue selenium levels show a complex pattern and significant elevations in organs such as kidney are not always indicative of toxicity. As with many trace elements, measuring selenium concentrations in body fluids and tissues tends to be easier than understanding what the results mean.

Keywords: trace elements, selenium toxicity, gun-bluing, mercury

Introduction

Selenium is an essential trace element in human metabolism, and like other trace elements, it is toxic at high concentrations [1]. Although selenium poisoning is not reported frequently in humans, incidents include industrial accidents [2], accidental ingestions, suicides, and attempted murder [3]. The question of murder with selenium has been raised in the popular press [4]. The present review provides a framework for the interpretation of elevated selenium concentrations in serum, postmortem blood, liver, kidney cortex, and heart, and is intended for pathologists, clinical chemists, and toxicologists who work in clinical laboratories.

There are several reasons why selenium poisoning can be difficult to evaluate. One reason is that selenium analysis is performed relatively infrequently, so experience with this analyte is often limited. There are few published case reports describing selenium poisoning, and those that have been published are seldom concerned about differentiating toxic from nontoxic elevations. There is also the problem that selenium is determined as its total concentration, despite the fact that different forms of selenium have much different degrees of toxicity [5-7]. Until the clinical laboratory gains the ability to speciate selenium into its many chemical forms, the evaluation of selenium poisoning is likely to remain stagnant.

Address correspondence to Kern Nuttall, M.D., Ph.D., 2112 Birch Circle, Bellingham, WA 98229, USA; tel 360 647 5212; e-mail: kern_nuttall@yahoo.com.

Nomenclature

Selenium is a nonmetallic element that is situated directly below sulfur on the periodic chart. Sulfur and selenium are notorious as volatile compounds associated with pungent odors, a fact that underscores their relationship. Since most laboratorians are unlikely to be familiar with the details of selenium chemistry, selected compounds relevant to the present discussion are listed in Table 1;

0091-7370/06/0400-409. $3.00. © 2006 by the Association of Clinical Scientists, Inc.

Table 1. Selenium and selected selenium compounds.

Primary name	Chemical formula	Notes
oxidation state +6		
selenium trioxide	SeO_3	white crystal, forms selenic acid in water
selenic acid	H_2SeO_4	pK_2 1.7 [6]
selenate	SeO_4^{-2}	predominate anion at pH 7
oxidation state +4		
selenium dioxide	SeO_2	white crystal, forms selenious acid in water
selenious acid	H_2SeO_3	pK_1 2.8, pK_2 8.5 [6]
selenite	SeO_3^{-2}	predominately $HSeO_3^{-1}$ at pH 7
oxidation state 0		
elemental selenium	Se_n	polyatomic chains, several allotropes [9]
colloidal selenium	Se_n	red-orange allotrope, forms in solution
selenium sulfides	Se_nS_n	mixture of the elements [9]
selenodiglutathione	GS-Se-SG	unstable metabolite of selenite [6]
oxidation state -2		
hydrogen selenide	H_2Se	volatile gas; pK_1 3.9, pK_2 11 [9]
sodium selenide	Na_2Se	crystal, slowly decomposes in air [9]
hydrogen selenide ion	HSe^{-1}	predominant anion at pH 7, unstable [50]
mercury(II) selenide	HgSe	extremely insoluble precipitate [51]
dimethylselenide	$H_3C\text{-}Se\text{-}CH_3$	volatile metabolite, garlic-like odor [6]

Table 2. Published reports discussed in text (with emphasis on selenium in postmortem blood and tissue).

Report	Age & Gender (yr, M/F)	Blood µg/L	Liver µg/g	Kidney µg/g	Heart µg/g	Notes
1	17 M	38000	741	450	234	fatal ~ 3 hr
2	44 M	18400	7.25	6.5		fatal ~ 1.5 hr[a]
3	24 M	13000	45	35	50	fatal ~ 4 hr[b]
4	2 M	12000				fatal ~ 4 hr
5	40 M	2600	24	64		fatal ~ 8 hr[b]
6	22 F	1430	19	15		fatal ~ 15 hr[b]
7	52 F		3.5		15	fatal at 8 d[b]
8	43 M		2.0	21		without toxicity[b]
9	adults		0.30-6.00			without toxicity[c]
10	adults		0.88-2.60	1.38-7.79	0.70-1.85	reference study[c]

[a]Inhalation.
[b]Tissue concentration estimated from wet weight (dry = 4.5 x wet).
[c]Total range from autopsy series.

alternative names can be found in sources such as the CRC Handbook [8] and the Merck Index [9]. When needed, formal oxidation states are indicated by Roman numerals; for example, selenium(VI) indicates the +6 oxidation state and is pronounced "selenium-six".

Like elemental sulfur, elemental selenium is polyatomic and has several allotropic states. Colloidal elemental selenium, also called amorphous selenium, is the allotrope that forms in aqueous solution, producing a red-orange precipitate (see Report 1). Selenium sulfides [9], often referred to in the singular, consist of variable proportions of elemental sulfur and selenium, depending on the manner of formulation.

Selenium can substitute for sulfur in numerous organic compounds [6]. One method for naming such compounds is to add the prefix "seleno" to the common name of the sulfur analog. Examples include selenocysteine (R-CH_2-Se-H, where "R" is the amino acid skeleton), selenocystine (R-CH_2-Se-S-CH_2-R), diselenocystine (R-CH_2-Se-Se-CH_2-R), and selenomethionine (R-CH_2-CH_2-Se-CH_3). An example of a selenotrisufide (-S-Se-S-) is selenodiglutathione (G-S-Se-S-G), an important intermediate in selenite metabolism. While this nomenclature has limitations, it is widely used and is applicable to most compounds of interest here.

In general, organoselenium compounds are more reactive than their sulfur counterparts. For example, selenocysteine is more acidic than cysteine (pK 5.2 vs 8.33) [9] and is more easily oxidized. Teleologically, this is one reason why selenocysteine is well-suited for the active sites of enzymes such as glutathione peroxidase.

Toxicity

For the present purposes, toxicity is characterized as acute or chronic. Acute poisoning typically involves a single dose that produces symptoms within min to hr, whereas chronic poisoning involves smaller doses given repeatedly, producing symptoms that become apparent over days or longer. Selenium toxicity is determined on the basis of signs and symptoms in the individual subject, not by laboratory values [10]. The strong garlic-like odor usually present in both acute and chronic poisoning is attributed to the volatile metabolite dimethylselenide [2,6]. This odor has also been described in the breath of individuals with sub-toxic exposure.

Different chemical forms of selenium can have vastly different toxic potentials. For example, when given orally to rats, the average lethal dose (LD_{50}) was 7 mg Se/kg body wt for sodium selenite, 138 mg Se/kg for selenium sulfides (as formulated for anti-dandruff shampoos), and 6700 mg Se/kg for elemental selenium [11].

Acute pattern. Early signs of acute toxicity include hypotension and tachycardia [5]. Early cardiac abnormalities often show T-wave flattening and inversion, and a prolonged QT interval (Reports 3 and 11). Death is typically preceded by refractory hypotension from peripheral vasodilatation and direct myocardial depression.

Nausea, vomiting, diarrhea, and abdominal pain are often present, and pulmonary edema can be a serious complication. Neurologic symptoms may include tremor, muscle spasms, restlessness, confusion, delirium, and coma. Ingestion of caustic compounds such as selenious acid often causes mucosal damage to the oral cavity, esophagus, and stomach. Laboratory abnormalities include elevated serum creatine kinase (CK) acivity, often appearing early and peaking at 4-5 days (Reports 7 and 15); the MB fraction of CK typically remains low.

Gun-bluing. Acute selenium poisoning often involves a commercial product used to stain metal a traditional gun-metal blue color. These gun-bluing agents typically contain formulations such as 2-9% selenious acid and 2-4% copper(II) in dilute acid. Although they are relatively high in copper and have sufficient acid to damage mucous membranes, the primary toxic agent is selenium.

Chronic pattern. Chronic selenium poisoning, or selenosis, often presents with nail changes and alopecia [12]. Other features may include nausea, vomiting, diarrhea, fatigue, and skin lesions. Peripheral paresthesias can be present, along with hyperreflexia and pain in the extremities. As selenosis progresses, decreased cognitive function, weakness, paralysis, and death can occur.

Nail changes are the most common sign of chronic selenium poisoning [12]. The nails become brittle, and white spots and longitudinal streaks appear on the surface. As chronic poisoning becomes more severe, breaks in the nail occur and the nail can be lost; nails may grow back deformed and be lost repeatedly. Fragile nails and similar changes are obviously not specific for selenosis, and other causes include fungal infection, psoriasis, and arsenic exposure. Nail changes are also unlikely to be the sole evidence of chronic selenium poisoning. When considering a patient with an elevated selenium concentration, the absence of characteristic nail changes is consistent with a lack of chronic poisoning.

Treatment. Although the treatment of selenium poisoning is not reviewed here, several points are worth emphasizing: (i) the most important aspects of treatment are supportive care and the prevention of further exposure, (ii) chelation is not recommended since animal studies suggest it may increase toxicity [13], and (iii) emesis is not recommended, particularly if a caustic compound such as selenite is involved [5].

Published Reports

To put selenium results into an appropriate context, published reports are summarized in Tables 2 and 3, and described briefly below (comments by the author are in parentheses); included are most case reports listed in Pub Med (www.pubmed.gov) as occurring in humans and published in English, and that have information on serum or postmortem blood selenium concentrations. Two animal studies are also summarized to emphasize aspects not as clearly illustrated in humans. The central theme drawn from the literature is not surprising and is merely this: the evaluation of selenium poisoning relies heavily on the clinical context.

Agents involved in reports of acute selenium poisoning are summarized in Table 4; all involve inorganic selenium(IV) or -(VI). (Reports of hydrogen selenide poisonings [14-16] did not contain information useful for the current review.) If the question of acute poisoning by other compounds arises, animal studies may be a useful source of information [5]. Routes of exposure other than ingestion are not adequately represented in the reports discussed here.

When comparing serum selenium results generated in different laboratories using different assays, it is reasonable to compare modestly elevated concentrations to within 1 significant figure, that is, 150-249 µg/L is about 200 µg/L. Analytic differences are probably less important at higher selenium concentrations.

Animal study A: acute selenite poisoning. The average lethal dose (LD_{50}) of sodium selenite given intramuscularly to sheep was 0.7 mg Se/kg [17]. The most consistent lesions were edematous lungs and pale mottled hearts. The highest tissue concentrations in declining order were in liver, kidney, and heart. As the dose increased, a larger proportion of the total dose was found in the heart.

Animal study B: selenium(VI) metabolism. Radiolabeled selenate (0.28-0.72 mg Se/kg) was given sc to rats [18]. The highest tissue level was found at 2 hr in the liver; this fell to about 13% at 24 hr. The peak value in kidney also occurred at 2 hr and fell to 20% at 24 hr. During the first day, >40% of labeled selenium was excreted in urine and 3-6% in feces.
(Since selenium concentrations decrease rapidly, the time from exposure to death can be an important variable when considering tissue. Selenite shows a similar pattern, although its metabolism is slightly more rapid [18].)

Report 1: massive ingestion of selenium dioxide. A 17 yr-old male was found comatose about 2 hr after ingesting 10 g of selenium dioxide reagent [19]. The patient was apneic and asystolic on admission, and was pronounced dead 45 min afterwards. Autopsy findings included edematous and distended lungs, diffuse swelling of the heart, edematous brain, and erosions of the esophageal and gastric mucosa. Selenium concentrations were 741 µg/g in liver, 450 µg/g in kidney, and 234 µg/g in heart (assumed to be dry weight because of the very high concentrations involved). "The most impressive finding was an intense orange-brown discoloration of the skin and all viscera" [19].
(The orange-brown discoloration is likely colloidal elemental selenium; its appearance is not described often, but it is consistent with the high level of exposure illustrated here. Deposits of colloidal selenium have also been described with hydrogen selenide exposure [2].)

Report 2: industrial fatality from fumes. A 44 yr-old worker was exposed to an eruptive mixture in a factory when selenic acid was neutralized too rapidly with sodium hydroxide [20]. He died 90 min later with symptoms of unstable blood pressure and pulmonary edema. A garlic odor was present on his breath. Findings on autopsy included hemorrhagic lung edema and dilation of the heart. Selenium in lung tissue was markedly elevated at 25 µg/g dry wt, but much lower in liver and kidney (Table 2). Death was attributed to respiratory insufficiency from pulmonary edema induced by inhalation of selenium fumes.
(As would be expected, inhalation and ingestion produce much different patterns of selenium distribution in tissues.)

Report 3: gun-bluing suicide in a male. A 24 yr-old male ingested about 55 mL of gun-bluing [21]. Cardiac monitoring 1 hr later showed sinus tachycardia with non-specific ST wave changes and a prolonged QT interval. His condition remained unchanged with persistent tachycardia and hypotension until cardiopulmonary arrest occurred about 4 hr after ingestion. A strong metallic garlic odor was noted at autopsy. The lungs were edematous, and the gastric mucosa showed diffuse hyperemia and focal hemorrhage. Selenium levels were 10, 7.8, and 11 µg/g wet wt in liver, kidney, and heart, respectively.
(This tissue pattern is different from the other acute poisonings in Table 2 in that selenium is much higher in heart tissue.)
Serum selenium was 30,000 µg/L in a specimen collected about an hr after ingestion; this probably represents an early distribution phase prior to equilibration. Selenium concentration in postmortem blood was 13,000 µg/L and probably

Table 3. Published reports discussed in text (with emphasis on serum selenium)

Report	Age & Gender (yr, M/F)	Dosing pattern	Serum Se (µg/L)	Notes
3	24 M	acute	30000	ingestion ~ 1 hr, fatal ~ 4 hr
7	52 F	acute	2435	ingestion at 4 d, fatal at 6 d
11	15 F	acute	3100	ingestion ~ 1 hr
12	56 M	acute	2716	ingestion ~ 3 hr
13	48 F	acute	2400	ingestion ~ 2 hr
14	2 F	acute	1580[a]	ingestion ~ 5 hr
15	29 M	acute	931[a]	ingestion ~ 3 hr
16	2 M	acute	420	ingestion at 1 d, fatal at 18 d
17	adults	chronic	650-1400[b]	no toxicity in 54 of 86
18	36 M	chronic	680	vitamin therapy for fatigue
19	57 F	chronic	528	nutritional supplement
20	adults	-	123-363[c]	without toxicity
21	≥14 M	-	101-151[d]	NHANES III reference interval

[a] Plasma.
[b] Range estimated from 65% of whole blood selenium.
[c] Range.
[d] 5th-95th percentile.

Table 4. Agents and estimated doses in acute poisonings

Report	Age & Gender (yr, M/F)	Patient weight (kg)	Agent	Amount	%Se	Estimated dose (mg Se/kg)
Fatal						
1	17 M	[a]	selenium dioxide	10 g	71	100
2	44 M		selenic acid			fumes
3	24 M	[a]	gun-bluing	[a] 55 ml	61	20
4	2 M	15	gun-bluing	9%, 15 ml	61	50
5	40 F	40	gun-bluing	4%, 90 ml	61	50
6	22 F	[a]	sodium selenate	[a] 20 ml	42	5
7[b]	52 F		gun-bluing			10-20[c]
16[b]	2 M	[a]	gun-bluing	[a] 15 ml	61	25
Non-fatal						
11	15 F		sodium selenate			22.3[c]
12	56 M	[a]	sodium selenite	1.7 g	46	10
13	48 F	[a]	selenium dioxide	2 g	71	20
14	2 F	11.6	gun-bluing	4%, 11 ml	61	20
15	29 M	[a]	selenic acid	3%, [a]	54	5

[a] Unknown variables assumed to be: 70 kg adult, 15 kg child, 4% solution, 20 ml volume.
[b] Delayed fatality.
[c] Dose from report.

represents redistribution into tissues more than clearance from the body. There is little difference between serum and whole blood selenium concentrations at these massive elevations.
(Given the rapid excretion of selenium seen in animal studies [18], the role of clearance could be larger than the authors suggest. However, they make an important point, namely, that early collection of serum tends to exaggerate the degree of exposure; after time for redistribution, concentrations are lower by perhaps as much as a factor of two.)

Report 4: fatal gun-bluing in a toddler. A 22 mo-old boy weighing 15 kg ingested about 15 mL of gun-bluing solution containing 9.3% selenious acid [22]. He was pronounced

dead <4 hr after ingestion. Autopsy findings included marked pulmonary congestion, hemorrhagic gastritis, and acute tubular necrosis. The cause of death was declared to be due to intractable ventricular fibrillation secondary to gun-bluing ingestion.
(While tissue analyses from this case would undoubtedly be interesting, the postmortem blood concentration listed in Table 2 is more than adequate for laboratory confirmation of acute selenium poisoning.)

Report 5: gun-bluing suicide in a female. A 40 yr-old female weighing 40 kg was admitted to the hospital an hr after ingesting about 90 mL of gun-bluing containing 4% selenious acid [23]. She was tachycardic and hypotensive on admission, and had cardiac arrest about 8 hr after ingestion. Autopsy revealed pulmonary edema, hemorrhagic stomach mucosa, and congestion of the kidneys and liver. Selenium levels were 5.4 µg/g wet wt in liver and 14.2 µg/g in kidney.
(This tissue pattern is different from the other acute poisonings in Table 2 in that selenium is much higher in kidney than liver. Also, the kidney selenium concentration is higher than in Report 3, even though the selenium concentration in postmortem blood is lower.)

Report 6: suicide with selenate. A 22 yr-old biology student suddenly developed abdominal pain, diarrhea, and vomiting [24]. In spite of intensive treatment, she developed cardiovascular failure and died 15 hr after her symptoms began. A "strange smell from her whole body" was noted. Just before dying, she confessed to ingesting about 20 ml of a sodium selenate solution. Postmortem examination revealed massive lung congestion, focal fibromatosis of the heart, cerebral edema, and focal necrosis of the gastric mucosa. Selenium levels were 4.20 µg/g wet wt in liver and 3.35 µg/g in kidney.

Report 7: gun-bluing with death on day 8. A 52 yr-old woman ingested several commercial products including 30-60 mL of gun-bluing [25]. The patient's clinical course included recurrent hypotension with low cardiac output, elevated pulmonary artery pressure, and low peripheral resistance. Early treatment included 2 doses of dimercaprol due to concerns of copper toxicity. Other features included diffuse weakness, hyporeflexia, poor bowel motility, thrombocytopenia, and mild renal insufficiency. Serum creatine kinase peaked on day 4 at 11,200 IU/L (reference interval 16-84); the MB fraction remained low. Serum selenium was 2435 µg/L on day 4 and 2763 µg/L on day 5.
(The selenium concen-trations appear discordant; however, presence of a chelating agent represents an unknown influence and Report 11 shows a similar pattern.)

The patient died after an extensive small bowel infarction on day 8. Autopsy revealed diffuse pulmonary edema and centrilobular liver congestion. Selenium concentration was markedly elevated at 3.36 µg/g wet wt in heart and relatively normal at 0.79 µg/g in liver.
(After 8 days, the selenium concentration in liver is consistent with the rapid metabolism seen in mice [18]; postmortem blood would probably also appear essentially normal. The more persistent elevation in heart tissue appears consistent with studies in sheep [17].)

Report 8: occupational mercury exposure. Correlations between tissue levels of selenium and mercury have been recognized for some time. After a 43 yr-old thermometer worker committed suicide by shooting himself in the head, tissue was collected for both mercury and selenium analysis [26]. Selenium was 0.451 µg/g wet wt in liver and 4.6 µg/g in kidney cortex (Table 2). The markedly elevated selenium content in kidney was associated with a co-accumulation of mercury.
(The chemical form responsible for the accumulation of selenium in a nontoxic state remains unsettled, but the phenomenon is well-documented. For example, an autopsy study in retired mercury miners showed markedly elevated selenium in kidney, thyroid, and pituitary tissue [27]. The fact that mercury exposure in retired miners had ceased many years earlier indicates that significant selenium elevations in some tissues can be both nontoxic and extremely stable.)

Report 9: autopsies of Danes and Inuits. Tissue from normal livers were obtained at autopsy from 74 Danish Caucasians [28]. The liver selenium concentration showed a median of 1.40 µg/g dry wt (95th percentile 2.88, range 0.30-6.00). Five values were above the 95th percentile with the maximum occurring in a 55 yr-old male. Selenium levels in liver tissue from 50 Greenland Inuits showed a median of 2.07 µg/g dry wt (95th percentile 3.90, range 0.90-4.50). Four values were higher than the 95th percentile with the maximum in a 55 yr-old female. The differences between the Danish and Inuit populations appear to be due primarily to dietary intake. The authors concluded that dietary selenium appears to be efficiently absorbed in humans and is not under homeostatic control.
(Sporadic elevations of liver selenium were found relatively frequently in the populations studied, free of any apparent toxicity.)

Report 10: autopsy reference study. Tissues were obtained from autopsy of 200 individuals of European descent born in the Netherlands [29]. Selenium in liver (n = 151) showed a mean of 1.75 µg/g dry wt (SD ± 0.35, median 1.72, range 0.88-2.60). Selenium in kidney cortex (n = 138) showed a mean of 4.60 µg/g dry wt (SD ± 1.06, median 4.55, range 1.38-7.79). Selenium in heart (n = 76) showed a mean of 1.25 µg/g dry wt (SD ± 0.25, median 1.26, range 0.70-1.85). Selenium levels appeared normally distributed and those specimens outside the normal distribution were excluded to eliminate the effect of outliers. Tissues showing pathologic changes were also excluded.
(These high quality reference intervals and ranges are extremely valuable, and it is worth emphasizing that the authors were not studying toxicity and made no claim to be doing so. Excluding outliers was appropriate for the purposes of the study, but outliers can be very relevant to what is identified as a potentially toxic concentration in tissue.)

Report 11: attempted suicide with sheep drench. A 15 yr-old girl in New Zealand ingested sheep drench that contained sodium selenate at a dose estimated to be 22.3 mg Se/kg [30]. She was admitted to the hospital 45 min afterwards with a strong odor of garlic on her breath and suffering from frequent diarrhea. Serial monitoring showed T-wave inversion and a prolonged Q-T interval, which reached a maximum at 3 days and resolved over 2 weeks. Treatment included multiple doses of dimercaprol. Serum selenium was 3100 µg/L on admission, 0.21 µg/L on day 3, and 0.48 µg/L on day 4. The patient recovered and was discharged after 17 days.
(The initial serum specimen was probably collected during the early distribution phase and is likely to overestimate the degree of exposure. The selenium concentrations on days 3 and 4 appear discordant; however, the chelating agent is an unknown influence. Report 7 shows a similar phenomenon.)

Report 12: attempted suicide with selenite. A 56 yr-old man ingested 1.7 g of sodium selenite [31]. On admission 4 hr after ingestion, he was alert and complained of abdominal pain, nausea, and diarrhea. His breath had a strong garlic odor. Blood pressure was normal and clinical examination was unremarkable except for erythematous changes of the oropharyngeal mucosa. Cardiac monitoring showed transient T-wave inversion. Laboratory testing showed mild hypoxemia, mildly elevated serum creatinine, and transient hyperbilirubinemia. Serum selenium concentration was 2716 µg/L at 3 hr and 473 µg/L at 22 hr.

Report 13: attempted suicide with selenium dioxide. A 48 yr-old woman was admitted about 2 hr after ingesting 2 g of selenium dioxide used for stained glass manufacture [32]. She presented with mildly altered consciousness, stable vital signs, and a smell of garlic. She vomited bloody fluid and complained of epigastric pain. Endoscopy showed a non-perforating ulcer at the gastric angulus; eroded mucosa was seen throughout the oral cavity, esophagus, and stomach, but the duodenum appeared intact. Serum selenium concentration was 2400 µg/L on admission and 600 µg/L the following day. The patient was discharged after 16 days and no sequelae were observed during the following year.

Report 14: gun-bluing in a young girl. A 2 yr-old girl, weight 11.6 kg, was brought to the hospital because of incessant vomiting [33]. Subsequent investigation showed she had ingested ≤11 ml of gun-bluing containing 26.3 mg Se/ml (roughly equivalent to 4% selenious acid). After endoscopy did not show esophageal damage, it was concluded that only a few drops had actually been ingested. Vomiting stopped 4 hr after admission and the remaining clinical course was largely uneventful. Plasma selenium concentration was 1580 µg/L about 5 hr after ingestion and 560 µg/L 12 hr later. No sequelae were seen in the following 3 mo.

Report 15: accidental ingestion of selenic acid. A 29 yr-old man accidentally ingested a mouthful of a solution containing 30 g/L (3%) selenic acid [31]. He immediately felt retrosternal pain and vomited. Clinical examination 1 hr later was unremarkable and no abnormality was seen on endoscopy. Serum creatine kinase activity became moderately elevated on day 3 and returned to normal by day 6. Plasma selenium concentrations were 931 µg/L at 3 hr, 664 µg/L at 6 hr, and 466 µg/L at 12 hr. Based on these data, the elimination half-life was calculated to be 17.5 hr.

Report 16: gun-bluing with death at 17 days. A 2 yr-old boy drank about 15 ml of gun-bluing [34]. He was immediately given milk and vomited spontaneously. He was admitted to the hospital about 3 hr after ingestion, conscious but drowsy. Damage to the esophagus and stomach was seen on endoscopy. Coma developed and he had to be ventilated mechanically. The clinical course included metabolic acidosis, cardiac arrhythmia, and moderate pulmonary, hepatic, and renal dysfunction. Urine selenium level was 28,459 µg/L shortly after admission and then fell rapidly.
(Aspects that make urine selenium levels difficult to evaluate include rapidly changing concentrations, unknown degrees of urine dilution, and the unknown time frame represent by the specimen.)

Serum selenium level was 420 µg/L on the day following admission and reached a normal value after 4 days. Although the boy was showing improvement, acute respiratory distress developed with extubation. *Legionella* was subsequently diagnosed and the patient died of pulmonary complications 17 days after ingestion.
(Although serum is an easier specimen to evaluate, a specimen collected this long after ingestion clearly underestimates the degree of selenium exposure and may represent only a minimal improvement over urine. After 17 days, postmortem blood and tissue would almost certainly have been within normal limits.)

Report 17: seleniferous region of China. Periodic outbreaks of selenosis have occurred in regions of China where high concentrations of selenium are found in the soil. Symptoms of selenosis were present in 32 of 86 individuals having whole blood selenium concentrations between 1000-2100 µg/L [10]. Selenosis was diagnosed on the basis of nail and hair changes, and was not seen in any of 228 individuals with whole blood selenium <1000 µg/L. The most serious cases were not found in those with the highest selenium concentrations and 9 asymptomatic individuals were identified who had whole blood selenium >2000 µg/L.
(See the discussion "Estimating serum from whole blood," below.)

Report 18: vitamins for fatigue. A 36 yr-old man developed alopecia, nail changes, and paresthesias after taking selenium-containing vitamin tablets for fatigue [35]. He was instructed to take 2 tablets every hr until he developed loose stools, and 10 tablets a day thereafter. During the first wk, he developed diarrhea, worsening fatigue, and hair loss. He discontinued the tablets after 2 wk. Several days later, his fingernails and toenails began developing yellowish-white and red transverse lines. Two wk after stopping therapy, the patient appeared well and with hair in an early stage of regrowth. Serum selenium level was 680 µg/L at that time. Although labeled as

containing 5 µg selenium per 6 tablets, analysis showed 500-1000 times that amount per tablet.
(The chemical species was presumably an organic form of selenium with a relatively long serum half-life. Stopping the exposure was the only intervention needed.)

Report 19: nutritional supplement. A 57 yr-old woman was taking daily selenium supplements for several wk before hearing that the brand was being recalled because of superpotency [36]. She had consumed 77 tablets labeled as containing 150 µg selenium, but which were subsequently found to contain 31 mg per tablet. (Eleven additional cases were later reported [37], although few details were provided.) Approximately 11 days after starting the supplement, the patient noticed marked loss of scalp hair; this progressed to almost total alopecia over 2 mo. She also complained of episodes of nausea and vomiting, "a sour-milk breath odor," and fatigue. Nail changes included white horizontal streaking, tenderness, swelling of the fingertip, and purulent discharge from the nail bed. The alopecia was initially attributed to emotional stress and the nail changes were treated with oral erythromycin for paronychia. Four days after stopping the tablets, her serum selenium level was 528 µg/L.

Report 20: seleniferous region of the US. In 142 adults living on farms in seleniferous regions of South Dakota, the range of serum selenium was 123-363 µg/L (mean 197, SD ± 55, median 184) [38]. Study subjects were examined with special attention to nail changes, paresthesias, and abnormal liver function tests, but no evidence of selenium toxicity was found. The corresponding selenium concentrations in whole blood were 182-674 µg/L (mean 319, SD ± 110, median 282). The Pearson correlation between whole blood and serum was 0.97. (The relationship "serum selenium = 0.65 x whole blood selenium" is based on median values from this report.)

Report 21: serum reference intervals. In the 3rd National Health and Nutrition Examination Survey (NHANES III), serum selenium (5th-95th percentile) was 101-151 µg/L (median 124) in 7102 US males ≥14 yr-old [39]. The corresponding reference interval for females was marginally lower at 98-150 µg/L (median 121). The maximum value in the study population was 425 µg/L (age and gender not reported) and was not associated with signs of toxicity.

Evaluation of Selenium Poisoning

While a massive elevation of serum selenium level in an acutely symptomatic patient is seldom a diagnostic dilemma, modest elevations are more frequent and tend to be more difficult to interpret. The evaluation of selenium poisoning ideally includes consideration of the signs and symptoms in the patient, the clinical history, and possible alternative diagnoses. Assessment of laboratory issues is discussed below.

Specimens. Serum is the specimen most responsive to rapid changes in selenium exposure and generally the most appropriate for evaluating poisoning [40, 41]; serum and plasma are equivalent for this purpose. Whole blood selenium is less useful because it responds more slowly, due to the influence of erythrocyte proteins [1]. Whole blood assay for glutathione peroxidase activity is not useful because the enzyme plateaus at normal selenium concentrations. While urine responds rapidly to selenium exposure (Report 16), it is more variable and more difficult to interpret [42]. Urine can be used to monitor occupational selenium exposures [2]; however, when the urine selenium level is elevated, serum is usually collected to evaluate the degree of selenium exposure [41]. When death intervenes and premortem serum is unavailable, postmortem blood is the most useful specimen to compare to published reports (Table 2). Tissue specimens can prove interesting, but the patterns are complex and may be difficult to interpret. The most frequently collected tissues are liver, kidney cortex, and heart.

Preanalytic specimen collection. While exogenous contamination is always a potential problem for trace elements [43], contamination is less of a problem for selenium [1,40-42]. Vaccutainer-type tubes are adequate for serum collection, assuming basic principles of environmental cleanliness are observed. Refrigeration appears adequate for storage [41]. A need for rapid freezing to avoid loss of volatile selenium compounds applies to urine specimens [5,44]. Repeated freezing and thawing denatures proteins and can alter the analytic result [41], although this is of more concern when small differences are important.

Postmortem blood. Collection of postmortem blood is influenced by a variety of factors that are seldom studied systematically [45,46]. Conditions that can affect the result include the location and method of specimen collection, and the time elapsed since death. These factors are likely to influence modest elevations of selenium levels more than the massive elevations listed in Table 2.

Tissue collection. Collection of tissue for selenium analysis does not require special precautions during

an autopsy [29]. However, the risk for exogenous contamination is increased by exposure to formalin, embalming fluids, exhumation, recovery from tissue blocks, and similar activities. Containers do not need to be acid-washed prior to tissue collection and any plastic container with a tight-fitting lid is probably suitable, provided it is clean and has not previously been used. Refrigeration or freezing are adequate for storage.

Selenium concentration in tissue is not significantly altered by the time since death or by the amount of blood present [29]. The selenium distribution appears to vary no more than 11% in liver, 8% in kidney cortex, and 5% in heart, although this applies only to normal tissue. Increased intra-organ variability may be more likely in pathologic tissue or when selenium is undergoing rapid metabolism, as in acute poisoning.

Analytic issues. Acceptable results are more likely to come from laboratories participating in an interlaboratory comparison program such as that offered by the Centre de Toxicologie du Québec (www.ctq.qc.ca). However, there is considerable variation even among such laboratories. For example, among the 33 laboratories participating in the first round of testing in 2006, a specimen of pooled human serum (E06-01) with a mean of 205 µg/L (CV 14%) showed a range of 126-269 µg/L [47]. Higher selenium concentrations tend to show less variation.

The measurement of selenium in clinical specimens is reviewed elsewhere [1,5,41,44], but several points are worth summarizing here. Since selenium can be present in many chemical forms, incomplete specimen digestion is a common source of error. Digestion must be vigorous while also avoiding the loss of volatile selenium compounds. Drying tissue at 120°C can result in appreciable loss of selenium content, >15% in oysters [48], but significant loss of selenium does not occur with lyophilization [40].

Tissue evaluation. When tissue selenium is determined as wet weight, the value can be converted to dry weight (Table 2) using the following relationship: dry wt = 4.5 x wet wt. This conversion factor was taken from Report 2 [20], where liver tissue was analyzed both before and after drying. This conversion factor is essentially the same as that used by Versieck [40] for the same purpose in a 1985 review of trace element reference intervals. Tissues other than liver show slightly different dry/wet ratios, but the differences tend to be small compared to uncertainties such as intra-organ variability. When comparing the results in Table 2, tissue concentrations are unlikely to be more accurate than one significant figure.

Animal studies indicate that kidney and liver selenium concentrations in acute poisonings drop >80% from peak values during the first 24 hr [18], although heart tissue remains elevated for longer periods (see Report 7). These rapid changes can be influenced by more stable forms of selenium, as is evident in Reports 8 and 9. It is tempting to speculate that the tissue pattern of selenium levels in Report 5 is due to acute poisoning superimposed on a stable elevation in kidney. Insufficient information is available to offer speculation about the pattern observed in Report 3.

Estimating serum selenium levels from whole blood levels. Serum selenium can be estimated from whole blood concentrations using the following relationship: serum selenium = 0.65 x whole blood selenium. The conversion factor was taken from Report 20 [38] and can only be regarded as approximate. Slightly different conversion factors can be derived from similar data, for example 0.75 [49], which emphasizes the degree of error in the approximation. While serum and whole blood selenium concentrations typically show a Pearson correlation of 0.97 [38], this applies to conditions where selenium exposure is relatively stable; this does not apply to acute poisoning.

Reference intervals. The reference interval is a measure of the selenium distribution in the population studied and is unrelated to the point at which toxicity develops. Signs of toxicity develop in most individuals only at some point higher than the upper reference limit. For occupational exposure, an upper limit of 100 µg/L for urine selenium has been recommended [2]. Like reference intervals, such recommended limits do not define toxicity, but are intended to limit exposure to levels

generally recognized as permissible for specific circumstances.

When considering reference intervals for selenium in tissue from autopsy studies, it may be appropriate to use the total range for comparison to case reports, as was done for Reports 9 and 10 in Table 2. This presumes that the patients involved died from causes unrelated to selenium and that all values reflect non-toxic concentrations, even those in the highest 1% of the study population. Using the reference interval for comparison will tend to exaggerate the degree of elevation in these circumstances, whereas the range will make an elevation appear more moderate and is presumably closer to where selenium toxicity might be anticipated. However, the same issue applies to both reference intervals and total ranges, namely, neither defines toxicity.

Exposure time. The time between exposure and specimen collection is an important variable when evaluating serum selenium levels in acute poisoning (Table 3). The degree of exposure tends to be exaggerated when serum is collected during the initial hr (Reports 3 and 11), whereas exposure can be seriously underestimated (Reports 7 and 16) when collection is delayed. Using the selenium half-life from Report 15 [31], the present author explored defining a uniform exposure time to facilitate comparisons among the acute poisoning cases. However, several problems arose. For example, the selenium concentration in Report 7 appears more stable than expected, making calculations based on the half-life unlikely to be accurate. It seems unlikely that the half-life would apply to the early distribution phase in Reports 3 and 11. In brief, calculating a uniform exposure time did not prove practical in this review.

Estimated dose. In Table 4, the dose was calculated by multiplying the amount of compound ingested (converted to mg) by the selenium content (%Se/100) and dividing by patient weight; estimates were given to one significant figure unless provided in the original report. Higher doses were associated more frequently with fatalities, although several cases do not fit the expected pattern. In Report 6, for example, the concentration of sodium selenate solution was unknown and the estimated concentration provided in the Table (4% or 4 g/100 ml) clearly underestimates the dose. Rather than make an independent guess for each piece of unknown information, Table 4 was compiled based on uniform approximations.

In Report 14, the amount of gun-bluing accidentally ingested was initially estimated to be about 11 ml, but was subsequently reduced to a few drops based on the clinical outcome. This seems to be a reasonable conclusion since the outcome is obviously the more important measure, but this process is also somewhat circular: the dose is estimated to help predict the outcome, then the outcome is used to re-evaluate the dose. While estimating the dose tends to be an error-prone process that is subject to circular logic, there are circumstances where it may be interesting.

Conclusions

The diagnosis of selenium poisoning is based on findings in the patient and is supported by laboratory analysis. Serum is generally the most useful specimen to evaluate selenium poisoning and the easiest to compare to published reports (Table 3). Elevated serum concentrations <1400 µg/L can be associated with acute poisoning, chronic poisoning, or can be free of toxicity; the category is determined by the clinical findings in the patient.

When unexplained symptoms are present, alternative diagnoses to selenium poisoning become more likely as selenium concentrations approach population norms. While exogenous contamination is less of a problem for selenium than for many other trace elements, contamination remains a possible cause, particularly when an isolated elevation of selenium concentration is unsupported by other findings.

Postmortem blood selenium concentration >1400 µg/L is consistent with acute poisoning as the cause of death during the initial day of exposure. Lower concentrations are more likely to be influenced by preanalytic collection artifacts, which may justify closer scrutiny. Tissue selenium concentrations can be interesting but are often difficult to evaluate.

Acknowledgement

The author was a consultant to the Fresno County Corner's Office regarding the suspected murder by selenium poisoning referred to in a 2005 television news report [4 ABC News 2005] and on a website http://www.whopoisonedlinda.com.

References

1. Lockitch G. Selenium: clinical significance and analytical concepts. Crit Rev Clin Lab Sci 1989;27:483-541.
2. Glover JR. Selenium and its industrial toxicology. Ind Med Surg 1970;39:50-54.
3. Ruta DA, Haider S. Attempted murder by selenium poisoning. BMJ 1989;299:316-317.
4. ABC News. Was a Young Mother's Death Murder? Television broadcast May 27, 2005. http://abcnews.go.com/2020/story?id=797262&page=1 as accessed June 24, 2006.
5. Agency for Toxic Substances and Disease Registry (ATSDR). Toxicological Profile for Selenium. U.S. Department of Health and Human Services, Public Health Services, Atlanta, GA, 2003. http://www.atsdr.cdc.gov/toxprofiles/tp92.html.
6. Barceloux DG. Selenium. J Toxicol Clin Toxicol 1999;37:145-172.
7. Thomson CD. Selenium speciation in human body fluids. Analyst 1998;123:827-831.
8. CRC Handbook of Chemistry and Physics, 76th ed. CRC Press, Boca Raton, FL, 1995.
9. Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals, 12th ed. Merck, Whitehouse Station, NJ, 1996.
10. Whanger P, Vendeland S, Park YC, Xia Y. Metabolism of subtoxic levels of selenium in animals and humans. Ann Clin Lab Sci 1996;26:99-113.
11. Cummins LM, Kimura ET. Safety evaluation of selenium sulfide antidandruff shampoos. Toxicol Appl Pharmacol 1971:20:89-96.
12. Yang G, Wang S, Zhou R, Sun S. Endemic selenium intoxication of humans in China. Am J Clin Nutr 1983;37:872-881.
13. Paul M, Mason R, Edwards R. Effect of potential antidotes on the acute toxicity, issue disposition and elimination of selenium in rats. Res Commun Chem Pathol Pharmacol 1989;66:441-450.
14. Alderman LC, Bergin JJ. Hydrogen selenide poisoning: an illustrative case with review of the literature. Arch Environ Health 1986;41:354-358.
15. Schecter A, Shanske W, Stenzler A, Quintiliana H, Steinberg H. Acute hydrogen selenide inhalation. Chest 1980;77:554-555.
16. Banerjee BD, Dwivedi S, Singh S. Acute hydrogen selenide gas poisoning admissions in one of the hospitals in Delhi, India: case report. Hum Exp Toxicol 1997;16:276-278.
17. Blodgett DJ, Bevill RF. Acute selenium toxicosis in sheep. Vet Hum Toxicol 1987;29:233-236.
18. Bopp BA, Sonders RC, Kesterson JW. Metabolic fate of selected selenium compounds in laboratory animals and man. Drug Metab Rev 1982;13:271-318.
19. Koppel C, Baudisch H, Kloppel I. Fatal poisoning with selenium dioxide. J Toxicol Clin Toxicol 1986;24:21-35.
20. Schellmann B, Raithel HJ, Schaller KH. Acute fatal selenium poisoning. Arch Toxicol 1986;59:61-63.
21. Hunsaker DM, Spiller HA, Williams D. Acute selenium poisoning: suicide by ingestion. J Forensic Sci 2005;50:1-5.
22. Quandrani DA, Spiller HA, Steinhorn D. A fatal case of gun blue ingestion in a toddler. Vet Human Toxicol 2000;42:96-98.
23. Matoba R, Kimura H, Uchima E et al. An autopsy case of acute selenium (selenious acid) poisoning and selenium levels in human tissues. Forensic Sci Int 1986;31:87-92.
24. Lech T. Suicide by sodium tetraoxoselenate(VI) poisoning. Forensic Sci Int 2002;130:44-48.
25. Pentel P, Fletcher D, Jentzen J. Fatal acute selenium toxicity. J Forensic Sci 1985;30:556-562.
26. Barregard L, Sallsten G, Conradi N. Tissue levels of mercury determined in a deceased worker after occupational exposure. Int Arch Occup Environ Health 1999;72:169-173.
27. Falnoga I, Tusek-Znidaric M, Horvat M, Stegnar P. Mercury, selenium, and cadmium in human autopsy samples from Idrija residents and mercury mine workers. Environ Res 2000;84:211-218.
28. Milman N, Laursen J, Byg KE et al. Elements in autopsy liver tissue samples from Greenlandic Inuit and Danes. V. Selenium measured by X-ray fluorescence spectrometry. J Trace Elem Med Biol 2004;17:301-306.
29. Aalbers TG, Houtman JPW, Makkink B. Trace-element concentrations in human autopsy tissue. Clin Chem 1987;33:2057-2064.
30. Civil ID, McDonald MJ. Acute selenium poisoning: case report. NZ Med J 1978;87:354-356.
31. Gasmi A, Galliot-Guilley M, Gaudillat C et al. Acute selenium poisoning. Vet Human Toxicol 1997;39:304-308.
32. Kise Y, Yoshimura S, Akieda K et al. Acute oral selenium intoxication with ten times the lethal dose resulting in deep gastric ulcer. J Emerg Med 2004;26:183-187.
33. Lombeck I, Menzel H, Frosch D. Acute selenium poisoning of a 2-year-old child. Eur J Pediatr 1987;146:308-312.
34. Nantel AJ, Brown M, Dery P, Lefebvre M. Acute poisoning by selenious acid. Vet Hum Toxicol 1985;27:531-533.
35. Clark RF, Strukle E, Saralyn W, Manoguerra AS. Selenium poisoning from a nutritional supplement. JAMA 1996;275:1087-1088.
36. Centers for Disease Control. Selenium intoxication -- New York. Morb Mortal Wkly Rep 1984;33:157-158.
37. FDA. Toxicity with superpotent selenium. FDA Drug Bulletin 1984;14:19.

38. Longnecker MP, Taylor PR, Levander OA, Howe SM, Veillon C, McAdam PA, Patterson KY, Holden JM, Stampfer MJ, Morris JS, Willett WC. Selenium in diet, blood, and toenails in relation to human health in a seleniferous area. Am J Clin Nutr 1991;53:1288-1294.
39. Kafai MR, Ganji V. Sex, age, geographical location, smoking, and alcohol consumption influence serum selenium concentrations in the USA: Third National Health and Nutrition Examination Survey, 1988-1994. J Trace Elem Med Biol 2003;17:13-18.
40. Versieck J. Trace elements in human body fluids and tissues. Crit Rev Clin Lab Sci 1985;22:97-184.
41. Sheehan TMT, Halls DJ. Measurement of selenium in clinical specimens. Ann Clin Biochem 1999;36:301-315.
42. Iyengar V, Woittiez J. Trace elements in human clinical specimens: evaluation of literature data to identify reference values. Clin Chem 1988;34:474-481.
43. NCCLS. Control of Preanalytical Variation in Trace Element Determinations; Approved Guideline – 2nd ed. NCCLS document C38-A2. NCCLS, Wayne, PA, 2001.
44. Bem EM. Determination of selenium in the environment and in biological material. Environ Health Perspect 1981;37:183-200.
45. Cook DS, Braithwaite RA, Hale KA. Estimating antemortem drug concentrations from postmortem blood samples: the influence of postmortem redistribution. J Clin Pathol 2000;53:282-285.
46. Drummer O, Forrest ARW, Goldberger B, Karch SB. Forensic science in the dock. Br Med J 2004;329:636-637.
47. Centre de Toxicologie du Québec. Interlaboratory comparison program for metals in biological samples 2006; report for run #1, p 47-48. http://www.ctq.qc.ca.
48. Fourie HO, Peisach M. Loss of trace elements during dehydration of marine zoological material. Analyst 1977;102:193-200.
49. Hansson L, Pettersson J, Eriksson L, Olin A. Atomic absorption spectrometric determination of selenium in human blood components. Clin Chem 1989;35:537-540.
50. Nuttall KL, Allen FS. Kinetics of the reaction between hydrogen selenide ion and oxygen. Inorg Chim Acta 1984;91:243-246.
51. Aylett BJ. The chemistry of zinc, cadmium and mercury. In: Comprehensive Inorganic Chemistry. Pergamon, New York, 1973; p 311.